REMARKS

In view of the following remarks, the Applicant respectfully requests allowance of Claims 1-4, 6-7, 9-12, 14-16, and 26-28 and 30, the only claims pending and under consideration in this application.

Formal Matters

Claims 1, 10 and 26 are amended. Support for these amendments are found throughout the specification, for example, page 3, lines 9-12, page 13, lines 13-21, page 16, lines 18-23, page 17, lines 20-24, and page 24, lines 1-6 and in original Claims 6, 8 and 29.

Claims 8, 13 and 29 are canceled.

As no new matter is added by way of these amendments, entry by the Examiner is respectfully requested.

Claim Rejections – 35 USC § 112, 2nd paragraph

Claims 1-4, 6-16, and 26-30 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. The Applicant respectfully traverses this rejection.

In formulating this rejection, the Examiner asserts that Claims 1 and 26 are indefinite because step (c) of these claims recite one or more groups of probes that exhibit "substantially the same performance" across a plurality of experiments and (d) recites identifying probes by evaluating probes that are not among these groups. The Examiner states that it is confusing to him why the probes not amongst the consistent performers were evaluated for their suitability as normalization probes. The Examiner further states that for the purposes of examination, claims 1 and 26 are interpreted as reciting identifying probes from groups that exhibit consistent performance.

The Applicant disagrees with the Examiner's interpretation of claims 1 and 26. However, solely to expedite the prosecution of this application claims 1 and 26 are amended to clarify that step (c) and (d) of claims 1 and 26 require:

(c)   clustering said candidate probe sequences into one or more groups of candidate probe sequences based on each candidate probe sequence's collection of empirical gene expression data values, wherein each of said one or more groups includes candidate probe sequences which exhibit substantially the same performance across said differential gene expression assay experiments, wherein candidate probe sequences in said one or more groups detect differential expression of said target nucleic acid in said at least one sample pair;

(d)   identifying any sequences of nucleic acids that are suitable for use as substrate surface immobilized normalization probes from said plurality of candidate probe sequences, comprising evaluating any remaining candidate probe sequences not among said one or more groups of candidate probe sequences for candidate probe sequences that satisfy a signal intensity threshold and exhibit substantially no change in signal across said differential gene expression assay experiments.

The Applicant believes that the metes and bounds of the rejected claims are apparent to one of skill in the art. Accordingly, this rejection may be withdrawn.

Claim Rejections - 35 USC § 103: Collins and Lockhart

Claims 1-3, 6-9, 14-16, and 26-30 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Collins (US Patent Application No. 2004/0101846; filed November 22, 2002), in view of Lockhart (US 6,344,316, issued February 5, 2002). The Applicant respectfully traverses this rejection.

35 U.S.C. § 103 (a) states that a patent may not be obtained if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made[1]. However, 35 U.S.C. § 103 (c) states that subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under § 103(a) where the subject matter and the

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[1] 35 U.S.C. § 103(a) : A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

The instant application was filed on October 14, 2003. Collins qualifies as prior art only under 102 (e) because its filing date of November 22, 2002 precedes that of the instant application, whereas its publication date is after the filing date of the instant application.

Since Collins qualifies as prior art only under 102 (e), according to 35 USC § 103(c), the Collins patent application cannot preclude the patentability of the rejected claims if the Collins patent application and the instant application were assigned to the same person or subject to an obligation of assignment to the same person, at the time the instant invention was made.

The invention claimed in the instant patent application was owned by Agilent Technologies, Inc. ("Agilent") or subject to an obligation of assignment to Agilent at the time the instant invention was made, as evidenced by an assignment executed by the inventors (Reel/Frame 014563/0683). This assignment was recorded on 04/26/2004.

The Collins patent application was owned by Agilent or subject to an obligation of assignment to Agilent at the time the instant invention was made, as evidenced by assignments executed by the inventors (Reel/Frame 013595/0913). This assignment was recorded on 04/24/2003.

Thus, the Collins patent application and the claimed invention were, at the time the invention was made, assigned or under obligation of assignment to Agilent. Accordingly, Collins patent application cannot preclude patentability of the instant claims under § 103(a).

In view of the above, the Collins patent application cannot be used to preclude patentability of the claimed invention of the subject application under § 103(a).

Since Lockhart is cited solely for its alleged teachings of a normalization probe, Lockhart, standing alone, cannot render the rejected claims obvious.

Accordingly, the Applicant respectfully requests the withdrawal of this rejection.

Claim Rejections - 35 USC § 103: Li, Relogio and Ben-dor

Claims 1, 2, 6-10, 12-16 and 26-30 are rejected under 35 U.S.C. § 103(a) as

allegedly being obvious over Li et al. (Bioinformatics, 2001, v. 17 p.1067; "Li") in view of Relogio et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-10; "Relogio") and Ben-dor et al. (J. Comp. Biol., v. 6 p. 281; "Ben-dor"). The Applicant respectfully traverses this rejection.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. S*ee, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, *e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740; emphasis added . As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The claimed invention is drawn to methods of identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe. The claimed methods include an empirical evaluation step in which candidate probes for a target nucleic acid are immobilized on a substrate in an array format, subjected to different experimental conditions that include differential gene expression assays to produce empirical gene expression data values. Each of the differential gene expression assays employs a different nucleic acid sample pair, where the target is differentially expressed in at least one sample pair. These empirical gene expression data values are then employed to cluster the candidate probe sequences into groups, where each of the one or more groups includes candidate probe sequences which exhibit substantially the same performance across said differential gene expression assay experiments, where candidate probe sequences in the one or more groups detect differential expression of the target in at least one sample pair. Candidate probes not among these groups are evaluated for candidate probe sequences that satisfy a signal

intensity threshold and exhibit substantially no change in signal across the differential gene expression assay experiments to identify suitable normalization probes.

The Applicant submits that a *prima facie* case of obviousness is not established as none of the cited references, individually or in any combination, teach or suggest all the claim elements. Specifically, Applicants submit the combination of Li, Relogio and Ben-dor fails to teach or suggest the following steps included in the instant claims:

(c)   clustering said candidate probe sequences into one or more groups of candidate probe sequences based on each candidate probe sequence's collection of empirical gene expression data values, wherein each of said one or more groups includes candidate probe sequences which exhibit substantially the same performance across said differential gene expression assay experiments, wherein candidate probe sequences in said one or more groups detect differential expression of said target nucleic acid in said at least one sample pair;

(d)   identifying any sequences of nucleic acids that are suitable for use as substrate surface immobilized normalization probes from said plurality of candidate probe sequences, comprising evaluating any remaining candidate probe sequences not among said one or more groups of candidate probe sequences for candidate probe sequences that satisfy a signal intensity threshold and exhibit substantially no change in signal across said differential gene expression assay experiments.

In making this rejection, the Examiner asserts that Li teaches a computer-implemented method and program for selecting an optimal number of DNA oligonucleotides for gene expression arrays. The Examiner notes that Li does not specifically teach a step for empirically evaluating candidate probes. To remedy this deficiency, the Examiner cites Relogio for its teachings of empirical methods for evaluating microarray data under different experimental conditions and obtaining empirical data for probe sensitivity, specificity and dynamic range.

The Examiner notes that Li does not specifically teach limitations directed to evaluating gene expression data based on clustering. To remedy this deficiency, the Examiner cites Ben-dor, stating that it would have been obvious to someone of ordinary skill in the art to practice the array probe selection method of Li using the clustering method of Ben-dor to rapidly analyze gene expression data produced by candidate

probes in order to provide additional information for selecting optimal probes.

The Examiner further notes that Li does not teach step (d) of claims 1 and 26 but asserts that this limitation would have been obvious to the skilled artisan since Relogio identifies probes with signal intensity above and below a certain threshold (Table 2) and analyzes probes with no variation in probe intensity (Table 8) and the motivation would be to optimize selection of oligonucleotide probes to improve microarray performance, as suggested by Relogio.

The Applicant submits that contrary to the Examiner's assertion, Ben-dor does not teach or suggest clustering said candidate probe sequences for a target nucleic acid into one or more groups of candidate probe sequences, but rather teaches a clustering algorithm to analyze gene expression data (Abstract). Applications of this algorithm envisioned in Ben-dor include determining temporal gene expression patterns (p.290), multi-conditional expression analysis (p.291) and tissue clustering (p.294). Nowhere in Ben-dor is it taught or suggested that the clustering algorithm can be used to cluster candidate probe sequences for a single target nucleic acid into one or more groups. In all of the plurality of experimental conditions mentioned in Ben-dor, at no instance were the probes for a single target clustered based on each candidate probe sequence's collection of empirical gene expression data values. All of the teachings of Ben-dor are about clustering gene expression patterns and not about clustering candidate probes for a target nucleic acid as is required in step (c) of independent claims 1 and 26.

Furthermore, applicant submits that step (d) requires identifying sequences of nucleic acids that are suitable as substrate surface immobilized normalization probes. This step requires evaluating any remaining candidate probe sequences not among the one or more groups of candidate probe sequences for those that (i) satisfy a signal intensity threshold and (ii) exhibit substantially no change in signal across the differential gene expression assay experiments.

Relogio discloses methods for identification of optimal oligonucleotide probes that can discriminate a single nucleotide mismatch by ascertaining the effect of probe length, concentration, purity, attachment moiety, etc., on probe sensitivity and specificity (Abstract). As best understood by the Applicant, the Examiner is citing Table 2 of Relogio to show that Relogio is teaching how to identify probes that satisfy an intensity

threshold. However, Table 2 of Relogio (and, for that matter, any other section of Relogio) does not even teach identification of normalization probes, let alone identification of normalization probes using the method of the claimed invention. In fact, Relogio does not teach or suggest identifying normalization probes because Relogio already has a method for normalizing the data. Relogio uses spotting controls for normalization, i.e., a mix of oligonucleotides of known concentration labeled with Cy5 and Cy3 (see "Data Analysis" section on page 3, left column).

Moreover, the probes taught in Relogio do not "exhibit substantially no change in signal across said differential gene expression assay experiments", as required in the rejected claims. As best understood by the Applicant, the Examiner is citing Table 8 of Relogio to show that Relogio teaches this element. In Table 8, Relogio is presenting data that shows how well the probes that perfectly match the target mRNA (M) bind to the target as compared to probes with a mismatch (MM). Thus, the higher the ratio of M/MM, the better is the probe at discriminating between a single mismatch. Table 8 shows the percent of probes with a Match/Mis-match ratio>2 (M/MM>2) for binding to mRNA labeled with different protocols. Table 8 uses the probes specific to SXL gene as a negative control as the mRNA for this gene is not present in the mRNA used in the experiment. Relogio points out that the 25-mer probe and the oligo-dT primed cDNA as the combination that performs better than the 30 and 35mer probes. Thus, the probes evaluated in Table 8 do show a change in signal across different experimental conditions. Accordingly, table 8 does not show probes that "exhibit substantially no change in signal across said differential gene expression assay experiments", as required by the rejected claims.

Thus, Table 8 does not show a step that requires evaluating any remaining candidate probe sequences not among the one or more groups of candidate probe sequences for those that (i) satisfy a signal intensity threshold and (ii) exhibit substantially no change in signal across said differential gene expression assay experiments as claimed. Moreover, Relogio is not evaluating the probes using differential gene expression assay experiments. The targets for the probes come from a single source, i.e., Hela cells.

Thus, the combination of Li, Relogio and Ben-dor Relogio does not teach or suggest each and every claim element. Since Relogio does not even teach or suggest the element of evaluating probes that exhibit substantially no change in empirical gene expression data values across said differential gene expression assay experiments, step (d) of the instant claims cannot be obvious to a person of skill in the art.

Therefore, because the combined teachings of Li, Relogio and Ben-dor fail to teach of suggest each and every limitation of the claims, a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

Claim Rejections - 35 USC § 103: Sung, Relogio and Ben-dor

The Examiner has rejected Claims 1-4, 7-9, 13-16 and 26-30 under 35 U.S.C. § 103(a) as being obvious over Sung et al. (Proc. of Computational Systems Bioinformatics (CSB'03) August 11-14 2003, p. 1-10; "Sung") in view of Relogio, *supra*, and Ben-dor, *supra*.

Similar to the rejection above, the Examiner asserts that Sung's disclosed method of probe selection includes all elements of the claimed methods except the limitations directed to producing empirical gene expression data and evaluating gene expression using a clustering algorithm. To remedy the deficiency of producing empirical gene expression data, the Examiner cites Relogio. To remedy the lack of teaching of evaluating gene expression data based on clustering, the Examiner again cites Ben-dor. Regarding step (d) the Examiner, as discussed above, asserts that this step would be obvious to the skilled artisan in view of the teachings of Relogio at Table 2 and Table 8.

As argued above, the Applicant submits that the combination of Sung, Relogio and Ben-dor fails to teach steps c) and d) of the instant claims. Ben-dor does not teach clustering of candidate probes for a target nucleic acid, rather it teaches clustering of gene expression patterns. Relogio does not teach evaluating any remaining candidate probe sequences not among the one or more groups of candidate probe sequences for candidate probe sequences that (i) satisfy a signal intensity threshold and (ii) exhibit substantially no change in signal across said differential gene expression assay

experiments. Rather Relogio teaches methods for identifying optimal probes for an array. Moreover, the combination of the cited references fails to teach or suggest identifying normalization probes as required in the instant claims.

Therefore, because the combined teachings of Sung, Relogio and Ben-dor fail to teach or suggest each and every limitation of the claims, a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

Claim Rejections - 35 USC § 103: Li, Relogio, Ben-dor and Cao

The Examiner has rejected Claims 10 and 11 under 35 U.S.C. § 103(a) as being obvious over Li, *supra*, in view of Relogio, *supra*, and Ben-dor, *supra*, as applied to Claims 1, 2, 6-10, 12-16 and 26-30, above, and further in view of Cao et al. (Cross Comparison of DNA Microarray Platforms, Alliance for Cellular Signaling Laboratories, Sept. 26, 2003, p. 1-23; "Cao").

In making this rejection, the Examiner re-asserts that Li, Relogio and Ben-dor make obvious a method for selecting an optimal number of probes for use in gene expression arrays, as set forth above and applied to claims 1, 2, 6-10, 12-16 and 26-30.

The Examiner then asserts that while Li, Relogio and Ben-dor do teach the calculation of log-ratios of intensities, they do not teach or suggest the specific log-ratio limitations as set forth in claims 10 and 11.

To remedy this deficiency, the Examiner cites Cao, asserting that this reference teaches calculation of log-ratio values across a number of different experimental conditions and values, including values in the range of -0.16 to 0.44 as in claims 10 and 11.

However, as argued above, the Applicant submits that the combined teachings of Li, Relogio and Ben-dor fail to teach steps c) and d) of the instant claims. As Cao is cited merely for its teaching of log-ratio values, this reference fails to remedy this fundamental deficiency in the teachings of Li, Relogio and Ben-dor.

Therefore, because the combined teachings of Li, Relogio, Ben-dor and Cao fail to teach or suggest each and every limitation of the claims, a *prima facie* case of

obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Dave Scherer at (650) 833-7707.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10030468-1.

Respectfully submitted,

Date: December 17, 2008   By: /Shweta Chandra, Reg. No. 61,379/

Shweta Chandra, Ph.D.
Registration No. 61,379

Date: December 17, 2008   By: /David C. Scherer, Reg. No. 56,993/

David C. Scherer, Ph.D.
Registration No. 56,993

AGILENT TECHNOLOGIES, INC.
Legal Department, DL429
Intellectual Property Administration
P.O. Box 7599
Loveland, CO 80537-0599

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